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Using the Comprehensive Complication Index to rethink the ISGLS criteria for post-hepatectomy liver failure in an international cohort of major hepatectomies

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Abstract

Objective: To compare different criteria for post-hepatectomy liver failure (PHLF) and evaluate the association between International Study Group of Liver Surgery (ISGLS) PHLF and the Comprehensive Complication Index (CCI) and 90-day mortality.

Summary Background Data: PHLF is a serious complication following hepatic resection. Multiple criteria have been developed to characterize PHLF.

Methods: Adults who underwent major hepatectomies at twelve international centers (2010-2020) were included. We identified patients who met criteria for PHLF based on three definitions: 1) ISGLS, 2) Balzan (INR >1.7 and bilirubin >2.92 mg/dL) or 3) Mullen (peak bilirubin >7 mg/dL). We compared the 90-day mortality and major morbidity predicted by each definition. We then used logistic regression to determine the odds of CCI>40 and 90-day mortality associated with ISGLS grades.

Results: Among 1646 included patients, 19 (1.1%) met Balzan, 68 (4.1%) met Mullen, and 444 (27.0%) met ISGLS criteria for PHLF. Of the three definitions, the ISGLS criteria best predicted 90-day mortality (AUC=0.72; sensitivity 69.4%). Patients with ISGLS grades B&C were at increased odds of CCI>40 (grade B OR 4.0; 95% CI: 2.2-7.2; grade C OR 137.0; 95% CI: 59.2-317.4). Patients with ISGLS grade C were at increased odds of 90-day mortality (OR 113.6; 95% CI: 55.6-232.1). Grade A was not associated with CCI>40 or 90-day mortality.

Conclusions: In this diverse international cohort of major hepatectomies, ISGLS grade A was not associated with 90-day mortality or high CCI, calling into question the current classification of patients in this group as having clinically significant PHLF.

MINI-ABSTRACT

We used the Comprehensive Complication Index (CCI) to evaluate the ISGLS criteria for post-hepatectomy liver failure (PHLF) in a diverse, international cohort of major hepatectomy patients. We found that the designation of grades B and C PHLF captured a group of patients with substantial postoperative morbidity, while grade A PHLF was not associated with 90-day mortality or high CCI, calling into question this classification's clinical utility.

INTRODUCTION

Post-hepatectomy liver failure (PHLF) is a serious complication, and the most important determinant of mortality, following major liver resection.[1] Several factors contribute to an increased risk of PHLF, including patient comorbidities, hepatic steatosis and fibrosis, and future liver remnant. The incidence of PHLF reported in the literature ranges from 1.2 to 32%.[2] This wide range may reflect differences in preoperative liver pathology, patient demographics, and the criteria used to define PHLF.

Numerous definitions of PHLF have been proposed. In an analysis of 775 elective hepatic resections, Balzan et al. determined that patients who had a combination of prothrombin time index < 50% and serum bilirubin > 50 umol/L (50:50 criteria) on postoperative day 5 had a 59% percent risk of early postoperative mortality.[3] Sensitivity and specificity for in-hospital mortality were found to be 69.6% and 98.5%, respectively.[3] However, this criteria has been criticized for the use of arbitrarily defined cut-off values chosen based on the established Child score. Subsequently, Mullen et al. analyzed 1059 noncirrhotic patients undergoing hepatectomy and found peak bilirubin > 7 mg/dL to be the best predictor of 90-day mortality. They also evaluated the performance of the 50:50 criteria in their dataset and observed a substantially lower sensitivity of 50%.[4] It is important to note that this analysis excluded patients with cirrhosis, potentially calling into question the external validity of the peak bilirubin criteria.

More recently, the International Study Group of Liver Surgery (ISGLS) proposed a consensus definition of PHLF: increased INR with concurrent hyperbilirubinemia on postoperative day 5 (POD5) or later. This group also proposed a grading system (A-C) for the severity of PHLF based on its impact on clinical management, with grade A requiring no deviation from standard care, grade B requiring non-invasive deviation from normal postoperative clinical care, and grade C requiring invasive intervention.[2]

Several studies have been performed to evaluate the predictive validity of these definitions in external cohorts, with differing results. Existing literature is primarily based on single-center studies and multicenter studies with small proportions of major hepatic resections.[5,6]

The Comprehensive Complication Index (CCI) is a weighted score calculated based on the Clavien-Dindo grade of each complication experienced by a patient.[7] As such, it provides an estimation of the cumulative experience of a patient's morbidity.[8] While the CCI has been shown to provide an accurate and more holistic assessment of patient morbidity than the highest Clavien-Dindo complication grade,[9–11] no existing studies have evaluated definitions of PHLF with this measure.

This study aims to compare the ability of the ISGLS, Balzan, and Mullen criteria to predict 90-day mortality and morbidity in a large and diverse cohort of patients who underwent major hepatectomy. Furthermore, we will investigate the distribution of patient morbidity across grades of ISGLS using the CCI.

METHODS

This study was approved by the Institutional Review Board of the University of California San Francisco (IRB No: 20-31911).

Study Population

Patients were derived from a multicenter international cohort that includes patients who underwent liver resection between 2010 and 2020 from four centers in Europe, six centers in Japan, one center in the United Kingdom, and one center in the United States. Inclusion criteria were patient age 18 or over as well as major resection (≥ 3 segments, or ≥2 segments in the context of cirrhosis) at a participating center from 2010-2020. Both benign and malignant indications for surgery were included and surgical approaches included pure laparoscopic, robotic, hand-assisted, hybrid, and open liver resections. Both anatomical and non-anatomical hepatectomies were included. Exclusion criteria were preoperative portal vein embolization and two-stage hepatectomies. A complete case analysis was performed. Patients were included in the analysis if they had complete data for morbidity, mortality, and the lab parameters used to define PHLF.

Existing Definitions of PHLF

Patients were classified as meeting the Balzan criteria if total bilirubin was > 2.92 mg/dL and INR was > 1.7 on POD5.[3] Patients were classified as meeting the Mullen criteria if peak total bilirubin was > 7 mg/dL.[4] Patients were classified as meeting the ISGLS PHLF criteria if total bilirubin was > 1.2 mg/dL and INR was > 1.2 on POD5.[2] Patients who met ISGLS criteria were subsequently assigned grades A-C depending on the degree of deviation from the normal postoperative course. Grades were assigned based on complications experienced during the index admission.[2,12]

Outcomes

The primary outcome considered in this analysis was CCI. The CCI assigns each patient a score from 0 to 100, representing an aggregate measure of their postoperative morbidity.[8] Secondary outcomes included the highest Clavien-Dindo complication classification and 90-day mortality.[7] This time point is commonly used in the existing literature on PHLF as a shorter timeframe may incompletely capture mortality secondary to PHLF.[4]

Preoperative and Intraoperative Variables

Preoperative variables included patient age, sex, year of operation, ASA Physical Status classification,[13] Charlson Comorbidity Index,[14] clinical cirrhosis (Child-Pugh class), MELD score, tumor histology, liver histology, and previous abdominal surgery. Intraoperative variables included operative approach and the number of segments resected.

Statistical Analysis

Descriptive statistics were tabulated. Continuous variables were reported as medians with interquartile ranges. Categorical variables were expressed as counts and percentages. ISGLS, Balzan, and Mullen criteria for PHLF were evaluated with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), and area under the receiver operating characteristic curve (AUC) for prediction of 90-day mortality and major morbidity (defined as highest Clavien-Dindo grade 3-4).

To further investigate the burden of morbidity across ISGLS grades, we tabulated the distribution of CCI scores. Differences were assessed across ISGLS grades with the Kruskal-Wallis test and subsequent Dunn's pairwise comparison test with Bonferroni adjustment for multiple testing. We used logistic regression to determine the odds of a CCI score>40 and 90-day mortality associated with each ISGLS grade. The cutoff value of CCI >40 was selected based on its use in the existing literature and because it corresponds to the CCI value of one Clavien-Dindo grade IV complication. However, this threshold could also be reached as a result of multiple complications with lower Clavien-Dindo grades.[15,16]

We used logistic regression to evaluate the associations between pre-existing liver pathology and the subsequent development of grades B or C PHLF. Adjusted models included the following covariates: age, sex, year of operation, ASA, Charlson Comorbidity Index, number of segments resected, operative approach, previous abdominal surgery, and liver pathology (tumor histology, liver histology, prior chemotherapy, NAFLD). All analyses were conducted using STATA/IC version 16.1, and statistical significance was set at $p<0.05$.[17]

RESULTS

Clinicopathologic Characteristics of the Study Sample

Of the 2192 patients in the cohort, 546 (24.9%) were excluded due to missing data, leaving 1646 remaining for analysis (Table 1). The majority of patients were male (65%) and the most commonly reported indication for resection was hepatocellular carcinoma (32.4%), followed by colorectal liver metastases (26.2%) and cholangiocarcinoma (14.7%). The prevalence of clinical cirrhosis was 43.4%. The majority of patients had resection of 4 or more liver segments (62.5%).

Comparison of PHLF definitions by Major Morbidity and 90-day Mortality

While 444 patients met ISGLS criteria, only 19 met the Balzan criteria and 68 the Mullen criteria (Table 2). The ISGLS criteria had a higher sensitivity for major morbidity (41.5%; 95% CI: 35.7-47.5; compared to 6.0% for Mullen and 1.8% for Balzan). The odds ratio of major morbidity associated with meeting ISGLS criteria was 2.3 (95% CI: 1.7-2.9) with an AUC of 0.59.

The ISGLS criteria also had a higher sensitivity for 90-day mortality (69.4%, 95% CI: 57.5-79.8; vs 40.3% for Mullen and 12.5% for Balzan). Patients who met ISGLS criteria had 6.8 times increased odds of 90-day morality (AUC 0.72). Of note, the PPV for 90-day

mortality for the Mullen and Balzan definitions were higher than that of the ISGLS criteria (42.7%, 47.4%, respectively, vs 11.3% for ISGLS).

Comparison of ISGLS grades: CCI and 90-day Mortality

CCI increased with increasing ISGLS grade, with a median CCI of 8.7 for ISGLS grade A versus 100 for ISGLS grade C (Table 3). Post-hoc pairwise comparison revealed significant differences in median CCI across all groups ($p=0.005$ for grade A vs no PHLF, $p<0.001$ for all others). While ISGLS grades B and C were found to be associated with significantly increased odds of CCI>40, the association between ISGLS grade A and CCI>40 was not significant (OR 1.4, 95% CI: 0.8-2.4). Similarly, while grade C ISGLS was associated with an increased odds of 90-day mortality (OR 113.6, 95% CI: 55.6-232.1), ISGLS grade A was not found to have a significant association.

Association between Preoperative Liver Pathology and ISGLS Grades B and C PHLF

In unadjusted models, all malignant indications for resection were associated with increased odds of grades B/C PHLF, with cholangiocarcinoma having the highest odds (17.8; 95% CI: 4.3-74.6, Table 4). Steatosis, fibrosis and cirrhosis on histology, and NAFLD were all associated with significantly increased odds of PHLF. In adjusted models, associations with cholangiocarcinoma, fibrosis/cirrhosis, and NAFLD remained significant.

DISCUSSION

In this diverse international cohort of major hepatectomy patients, we found that the ISGLS definition of PHLF better predicts major postoperative morbidity and 90-day mortality compared to previously proposed criteria. Using CCI, we described a more granular picture of the distribution of morbidity across grades of ISGLS. We found that the designation of grades B and C PHLF captured a group of patients with substantial overall postoperative morbidity. In contrast, the finding that ISGLS grade A PHLF was not associated with 90-day mortality or high CCI may question this current classification's clinical utility. Finally, we found that NAFLD, fibrosis/cirrhosis on liver histology, and cholangiocarcinoma were strongly associated with developing grades B and C PHLF.

Following the development of the ISGLS criteria, several studies have sought to validate and compare existing definitions of PHLF, although with varied conclusions.[5,6,18,19] While Rahbari et al.'s single-center external validation of the ISGLS definition concluded that meeting ISGLS criteria was a strong independent risk factor for mortality,[18] Skrzypczyk et al.'s analysis of 680 non-cirrhotic patients concluded that the predictive ability of the ISGLS definition was inferior to previously proposed definitions on the basis of a lower positive predictive value.[5] More recently, Sultana et al. conducted an international multicenter study to evaluate the ISGLS definition compared to the Balzan and Mullen criteria and concluded that the ISGLS definition performed better on the basis of higher sensitivity.[6] Of note, all of these studies included both minor and major resections, with only 45% of the patients in Sultana et al's study having undergone resection of >3 segments. Our findings add to existing work by considering the performance of the ISGLS criteria in a multicenter cohort of patients who underwent major resection. It is important that evaluation of PHLF criteria

be conducted in studies with large numbers of major hepatectomies, as extent of resection is a well-established risk factor for PHLF.[6] Differences in extent of resection may also explain the higher prevalence of patients meeting criteria for PHLF in this analysis relative to other studies (26.8% in our study vs 9-12%).[5,18]

One of the novel aspects of this study is the use of CCI to analyze the ISGLS grading system. First proposed in 2013, CCI has gained traction as a holistic measure of postoperative morbidity. This stands in contrast to other measures of postoperative morbidity, such as highest Clavien-Dindo grade, which only consider the single most severe complication experienced. In addition, there is increasing evidence that the CCI may be superior to highest Clavien-Dindo grade in terms of its correspondence with postoperative factors such as hospital length of stay and financial burden.[9,11,20] While some studies have started to use CCI to measure complications following hepatectomy,[15,20] our paper is the first to use CCI to investigate the performance of the ISGLS criteria and grading system.

Our study found no association between ISGLS grade A and 90-day mortality or CCI>40, questioning the designation of ISGLS grade A as clinically meaningful PHLF. This differs from the findings of a previous single-center study of a cohort of predominantly minor hepatic resections.[21] The difference may stem from the clinicopathologic characteristics of these cohorts. We believe that the diversity of our cohort and greater proportion of major resections may provide a more robust source from which to evaluate the ISGLS grading system.

It is important to acknowledge that, for patients who experienced clinically evident PHLF, the Clavien-Dindo grade of PHLF contributes to overall CCI. Thus, we would expect median CCI to be higher for grades B and C relative to grade A, based on the ISGLS grading criteria. However, the median CCIs observed in both grades B and C PHLF were substantially higher than the level of complication inherent in the definition. For example, although ISGLS B is defined by non-invasive intervention, the median CCI in this group was 27.6, which is just above the CCI equivalent to one Clavien-Dindo 3a complication (i.e. invasive intervention). This suggests that patients in these PHLF grades encounter substantial postoperative morbidity above and beyond the direct sequala of their liver failure. Taken together, these findings suggest the need to reconsider the ISGLS grading system moving forward. Specifically, the range of morbidity observed in grade B suggests the need to further sub-stratify this category. In parallel, it may be reasonable to consider grade A not as liver failure, but as transient liver dysfunction. Future studies would be needed to develop and evaluate a revised ISGLS grading system.

Our findings of a strong association between NAFLD, histologic cirrhosis, cholangiocarcinoma and B and C PHLF are consistent with previous literature.[6,22] Biliary obstruction, a common sequela of cholangiocarcinoma, may account for some of the elevated risk of PHLF in these patients compared to other malignant diagnoses.

There are several limitations to our study. First, the retrospective nature of the study is subject to selection bias. Second, it is important to acknowledge the presence of missing data. We conducted a complete case analysis, and in doing so included 75% of the cohort.

However, the prevalence of 90-day mortality and morbidity was found to be similar between patients with complete data and those excluded due to missing data. Furthermore, this study did not collect laboratory data at routine intervals after POD5. This means that ISGLS liver failure was defined based on POD5 lab values, despite the formal definition specifying lab abnormalities "on or after" POD5.[2] It is possible that there were differences in patient selection and perioperative management by center. Readmission data were not uniformly available across centers and thus not included in this analysis. Consequently, we were unable to assess if patients developed PHLF or their ISGLS grade changed after their initial admission. Despite these limitations, our study's multicenter design including 12 expert liver centers and a large cohort of patients is a unique strength.

Conclusions

Overall, the application of the CCI to evaluate the ISGLS criteria for PHLF provides a more granular picture of the distribution of morbidity across grades of liver failure. These findings may be used to further refine the classification system, with a particular focus on reconsidering the clinical utility of ISGLS grade A. Although some studies already exclude grade A in their analysis, others consider all grades together as PHLF.[23,24] Furthermore, the range of postoperative morbidity experienced among those with grade B PHLF suggests that this category may be amenable to further sub-stratification. Ultimately, formalizing the distinction between grades could address inconsistent operationalization of PHLF in future studies and optimize our ability to develop models that accurately predict clinically meaningful liver failure.

Conflicts of Interest and Source of Funding:

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Table 1.

Clinicopathologic Characteristics of the Cohort (n=1,646)

Characteristic	Median (IQR) N (%)
Age	65 (55, 73)
Female:Male	577 (35.0): 1059 (65.0)
ASA	
I	320 (19.7)
II	933 (57.6)
III	353 (21.8)
IV	15 (0.9)
Charlson Comorbidity Index	4 (2, 7)
Clinical Cirrhosis	
None	932 (56.6)
Child A	689 (41.9)
Child B	23 (1.4)
Child C	2 (0.1)
MELD score	6 (6, 7)
Tumor histology	
No tumor (Living donor)	158 (9.6)
CRLM	431 (26.2)
HCC	534 (32.4)
CCC	242 (14.7)
Benign	167 (10.2)
Other malignancy	114 (6.9)
Liver histology	
Normal	742 (46.3)
Steatosis	395 (24.6)
Fibrosis/Cirrhosis	467 (29.1)
Previous abdominal surgery	
Yes	636 (39.0)
No	993 (61.0)
Approach	
Open	1421 (86.3)
Laparoscopic	217 (13.2)
Hand-assisted	8 (0.5)
Number of segments resected	4 (3, 5)

IQR: interquartile range; ASA: American Society of Anesthesiology physical status classification; CRLM: colorectal liver metastasis; HCC: hepatocellular carcinoma; CCC: cholangiocarcinoma

Table 2.

Comparison of Existing Definitions of PHLF (n=1,646)

		Balzan		Mullen		ISGLS		ISGLS *grades B&C*	
Major Morbidity [a]		**n=19**	***95% CI***	**n=68**	***95% CI***	**n=444**	***95% CI***	***n*=159**	***95% CI***
Sensitivity		1.77	*(0.58, 4.09)*	6.03	*(3.55, 9.48)*	41.49	*(35.68, 47.48)*	18.09	*(13.77, 23.08)*
Specificity		98.97	*(98.28, 99.44)*	96.26	*(95.11, 97.20)*	76.03	*(73.67, 78.27)*	*92.08*	*(90.52, 93.46)*
PPV		26.32	*(9.15, 51.20)*	25.00	*(15.29, 36.98)*	26.35	*(22.31, 30.71)*	*32.01*	*(27.60, 43.04)*
NPV		82.97	*(81.06, 84.77)*	83.21	*(81.27, 85.02)*	86.27	*(84.20, 88.17)*	*84.46*	*(82.52, 86.27)*
OR		1.74	*(0.62, 4.87)*	1.65	*(0.94, 2.90)*	2.25	*(1.72, 2.94)*	*2.57*	*(1.79, 3.69)*
AUC		0.504		0.511		0.588		*0.551*	
Mortality[b]									
Sensitivity		12.50	*(5.88, 22.41)*	40.28	*(28.88, 52.50)*	69.44	*(57.47, 79.76)*	*56.94*	*(44.73, 68.57)*
Specificity		99.37	*(98.83, 99.69)*	97.52	*(96.63, 98.23)*	74.97	*(72.75, 77.09)*	*92.50*	*(91.09, 93.76)*
PPV		47.37	*(24.45, 71.14)*	42.65	*(30.72, 55.23)*	11.26	*(8.47, 14.58)*	*25.79*	*(19.18, 33.31)*
NPV		96.13	*(95.07, 97.01)*	97.28	*(96.35, 98.02)*	98.17	*(97.24, 98.85)*	*97.91*	*(97.05, 98.58)*
OR		22.34	*(8.77, 56.92)*	26.54	*(15.04, 46.85)*	6.81	*(4.07, 11.38)*	*16.32*	*(9.87, 26.98)*
AUC		0.559		0.689		0.722		0.747	

[a] Major morbidity is defined as highest Clavien-Dindo grade 3-4.

[b] 90-day all-cause mortality

PPV: positive predictive value; NPV: negative predictive value; OR: odds ratio; AUC: area under the ROC curve; CI: confidence interval

Table 3.

Comparison of Morbidity and Mortality by ISGLS Grade (n=1,646)

	No ISGLS PHLF	ISGLS A	ISGLS B	ISGLS C	
	n=1,202	n=285	n=106	n=53	
CCI					
median (IQR)	0 (0-20.9) *	8.7 (0-26.2) *	27.6 (20.9-34.8) *	100 (50.7-100) *	p<0.001
CCI Category, N (%)					
CCI: 0	*674 (56.1)*	*138 (48.4)*	*0 (0)*	*0 (0)*	
CCI: 1-20	*104 (8.7)*	*19 (6.7)*	*13 (12.9)*	*0 (0)*	
CCI: 20-40	*369 (31.0)*	*110 (38.6)*	*76 (71.7)*	*7 (13.2)*	
CCI: 40-60	*33 (2.8)*	*9 (3.2)*	*13 (12.3)*	*9 (17.0)*	
CCI: 60-80	*2 (0.2)*	*0 (0)*	*0 (0)*	*1 (1.9)*	
CCI: 80-100	*20 (1.7)*	*9 (3.2)*	*4 (3.8)*	*36 (67.9)*	
CCI > 40					
OR (95% CI)	-	1.41 (0.81-2.43)	**3.98 (2.22-7.15)**	**137.04 (59.17-317.42)**	AUC=0.72
90-day mortality					
OR (95% CI)	-	1.75 (0.80-3.84)	2.66 (0.98-7.16)	**113.58 (55.59-232.07)**	AUC=0.78

* Dunn's multiple comparison test with Bonferroni adjustment revealed statistically significant differences between this value relative to all other categories.

ISGLS: International Study Group of Liver Surgery; PHLF: post-hepatectomy liver failure; CCI: comprehensive complication index; IQR: interquartile range; OR: odds ratio; CI: confidence interval

Table 4.

Association between Preoperative Liver Pathology and Grades B/C PHLF (n=1646)

	Univariate OR	95% CI	Adjusted OR [a]	95% CI
Tumor histology				
CRLM	**9.78**	**(2.33, 40.50)**	3.34	(0.67, 16.55)
HCC	**8.24**	**(1.98, 34.22)**	2.40	(0.50, 11.58)
CCC	**17.82**	**(4.26, 74.59)**	**6.38**	**(1.37, 29.70)**
Benign	1.43	(0.24, 8.65)	1.16	(0.18, 7.44)
Other malignancy	**7.50**	**(1.61, 34.93)**	2.12	(0.40, 11.34)
Liver histology				
Steatosis	**1.85**	**(1.20, 2.85)**	1.30	(0.80, 2.13)
Fibrosis/Cirrhosis	**2.26**	**(1.52, 3.37)**	**1.93**	**(1.15, 3.22)**
Chemotherapy	0.94	(0.58, 1.51)	0.60	(0.32, 1.09)
NALFD	**2.84**	**(1.55, 5.18)**	**2.31**	**(1.16, 4.62)**

[a] **Covariates:** age, sex, year of operation, ASA, Charlson Comorbidity Index, segments resected, operative approach, previous abdominal surgery

OR: odds ratio; CI: confidence interval; CRLM: colorectal liver metastasis; HCC: hepatocellular carcinoma; CCC: cholangiocarcinoma; NAFLD: non-alcoholic fatty liver disease